DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Biomedical Imaging and Bioengineering
Five-Year Professional Judgment Budget

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Executive Summary

In the House report 108-636, the Committee on Appropriations requested that the NIH develop a five-year professional judgment budget that would enable the NIBIB to grow at an appropriate rate. This document provides an overview of the rapidly developing research opportunities for the Institute and a professional judgment budget to meet those opportunities.

In the last quarter century, there has been a revolution that has brought engineering and imaging to greater prominence in the biomedical field. This revolution has had, and will continue to have, significant ramifications for medical practice. The National Institute of Biomedical Imaging and Bioengineering, the newest of the National Institutes of Health research Institutes and Centers, was created to provide a research home for the development and application of new and emerging technologies to improve health care in the 21st century. The Institute is positioned to further advance these fields through the support of technology development and promotion of interdisciplinary approaches to biomedical research.

This document outlines milestones and research directions in six scientific areas within the Institute's mission: image-guided interventions, molecular imaging, sensors and microsystems, nanotechnology and drug delivery, and tissue engineering. The document also addresses the Institute's interdisciplinary training programs. As the Institute evolves, the overarching goal will be to capitalize on emerging scientific areas where bioengineering, biomedical imaging, and related technology approaches can be used to develop more sensitive, more reliable, and more cost effective medical diagnostic and therapeutic systems. For example, research on image-guided interventions should lead to the development of new tools and technologies that will allow minimally-invasive, image-guided procedures to replace invasive surgical procedures as a new standard of care. Advances in molecular imaging and sensor technology will enable breakthroughs in the development of novel treatment modalities and lead to earlier and more accurate disease diagnosis with the ability to tailor therapies to individual patients. Research at the nanoscale will enhance the development of smart drug delivery systems capable of carrying potent drugs targeted to specific tissues or cells with minimal side effects. Tissue engineering will redefine approaches to tissue repair and transplantation through the creation of viable replacement tissues that are biological rather than synthetic. More broadly, engineered tissue will help provide novel solutions for drug screening and development, genetic engineering, and total organ replacement. Lastly, interdisciplinary training programs will lead to a new cadre of scientists capable of conducting the research required to produce these advances.

The creation of the NIBIB has occurred at a time of extraordinary scientific opportunity as multiple disciplines converge to advance technology development and its impact on health care. This professional judgment budget is based on the state of the science and the attendant opportunities in the major fields that the NIBIB supports; however, it was developed without consideration of economic constraints, unforeseeable scientific advances, or other competing priorities of the Federal government. Driving factors are both the Institute's mandate and commitment to accelerate discoveries and create and capitalize on opportunities to gain a greater understanding of disease and improve diagnostic and therapeutic tools. This will advance human health, reduce the burden of disease and improve the quality of life.

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Introduction

In its report on the fiscal year 2005 budget for the Department of Health and Human Services, the House Committee on Appropriations stated:

> The Committee recognizes the important role of new imaging and engineering techniques and technologies both in improving health care delivery and enabling progress in biomedical research. The Committee believes that NIBIB has worked effectively with the extramural community to identify important research opportunities and challenges. Through workshops and conferences, NIBIB has produced an ambitious research agenda that will produce new technologies with clinical applications to a broad spectrum of biological processes, disorders, and diseases and across organ systems as well as facilitate advanced research in virtually all other NIH Institutes. The NIH leadership has recognized the central role of imaging by including the development of molecular imaging and molecular libraries as an initiative in the NIH Roadmap for Medical Research. The important innovations envisioned in the imaging and biomedical engineering agenda are unlikely to be achieved in the foreseeable future, however, unless additional resources are available to NIBIB. Because NIBIB was created at the end of the congressional effort to double the NIH budget over 5 years, it faces special challenges as funding growth slows. The Committee urges the Director of NIH to give NIBIB special attention so that it can achieve its potential. For that reason, the Committee requests NIH to develop a 5-year professional judgment budget that would enable NIBIB to grow at an appropriate rate. The Committee expects to receive the report by May 1, 2005. (House Report 108-636, p. 98)

The following 5-year professional judgment budget has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request. It provides an overview of some of the exciting research opportunities in biomedical imaging and bioengineering along with a professional judgment budget for implementing a proactive research agenda to capitalize on these opportunities. However, this professional judgment budget was developed without consideration of economic constraints, unforeseeable scientific advances, or other competing priorities of the Federal government.

Background

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is the newest of the National Institutes of Health (NIH) research Institutes and Centers. Public Law 106-580, which was signed into law on December 29, 2000, authorized the establishment of the NIBIB to provide a research home for the development and application of new technologies and techniques for the delivery of health care in the 21st century. The NIBIB brings the research communities of biomedical imaging, bioengineering, and the physical sciences together with the life sciences community to advance human health by enabling technologies that improve the quality of life and reduce the burden of disease. The Institute's mission is to improve human health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the engineering and physical sciences with the life sciences to advance basic research and medical care.

This review of opportunities and five-year professional judgment budget builds from the first appropriation of $112 million in fiscal year (FY) 2002 and extends to FY 2009. In the last quarter century, there has been a revolution that has brought engineering and the physical sciences to greater prominence in the biomedical field. This revolution has had, and will continue to have, significant ramifications for medical practice. Sophisticated imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) have reduced the need for exploratory surgery. For example, CT imaging of the abdomen has dramatically reduced the use of exploratory surgery in the diagnosis of patients with suspected appendicitis. This is particularly significant in the pediatric population. Imaging for neurological tumors and trauma with CT and MRI reduced the need for exploratory operations and improved the identification and localization of disease thereby improving the effectiveness of such surgeries. Implanted therapeutic devices are increasingly used as effective treatments for cardiac rhythm abnormalities, joint dysfunction, and impaired neurological function. New biomaterials have led to a variety of novel therapies such as controlled release drugs that can be taken once a day and vascular stents that are resistant to clotting. In turn, these and other advances have fueled the worldwide growth of the medical device and diagnostics industry. This has become a rapidly evolving field that continues to yield dramatic improvements in the practice and delivery of health care.

Bioengineering has emerged as a vibrant discipline as a result of this revolution. Today there are more than 65 bioengineering departments at U.S. colleges and universities. There is also an increased emphasis on biomedical science in engineering and physical science departments. The fields of bioengineering and imaging will be further enhanced by multidisciplinary input from chemical, electrical, and mechanical engineers, as well as chemists and physicists.

Biomedical imaging is now an indispensable tool for the diagnosis and treatment of a variety of diseases. In the early 20th century, advances in imaging were achieved incrementally at a relatively slow rate. However, in the last 40 years, improvements and new discoveries in imaging technologies have occurred more rapidly. The X-rays of over 100 years ago have been followed by the discovery and further refinement of ultrasonic, radioisotope, optical imaging, computed tomography, and MRI as well-established diagnostic and therapeutic tools. In addition, the scalability of imaging methods is growing – ranging from visualization of the whole body and individual organs, to cellular, sub-cellular, molecular, and atomic imaging.

The creation of the NIBIB has occurred at a time of extraordinary scientific opportunity. Discoveries in biomedical imaging and bioengineering have already had an enormous impact on health care. These disciplines are dynamic and ripe with opportunities for major scientific advances. The NIBIB is well-positioned to capitalize on past and future discoveries and to accelerate the translation of these scientific advances to health care. This professional judgment budget describes how the NIBIB could lead advances in these expanding fields, respond to discoveries and opportunities, and ensure the best use of resources to benefit the public. The document outlines research advances and future research directions in six different areas that span the continuum of NIBIB programs.

Image-Guided Interventions

For most of the history of medicine, physicians relied on their senses – primarily vision and touch – to diagnose illness, monitor a patient's condition, and perform invasive procedures. Recent advances in biomedical imaging have radically expanded these approaches. Imaging devices, such as CT, MRI, and ultrasound now allow a physician to see and diagnose disease that is hidden from normal view.

The next paradigm shift that will occur involves the use of biomedical images during treatment or surgery, a concept referred to as image-guided interventions. Real-time, two-dimensional (2D) imaging is already used to guide treatment in many ways. For example, x-ray images are used to treat narrowed blood vessels in the heart and endoscopes are commonly used in abdominal and knee surgeries. However, a quantum leap in health care could be achieved if many more traditional surgeries and invasive treatments were replaced with minimally-invasive, image-guided interventions. Minimally-invasive treatments – which require only a small incision, or, in some cases, no incision – result in less damage to critical organs surrounding the surgical site, less postoperative pain, fewer surgical complications, shorter hospital stays, and lower health care costs.

The technology employed in today's operating rooms does not accommodate the real-time, three-dimensional (3D) imaging needs of surgeons. Today's 2D image technologies do not provide an adequate view to guide a surgeon's navigation to the desired site through small incisions. Moreover, the surgeon's direct line of sight is blocked, resulting in a visual disconnect from the surgical target of interest. For 3D views there are a variety of imaging devices which can guide minimally-invasive therapies by fusing images from different imaging devices, such as MRI, CT, and positron emission tomography (PET). These fused images allow the surgeon to have a clear view, even see through solid organs in order to reach the target area with minimal damage to the surrounding organs. Furthermore, integrating 3D images with semi-autonomous devices, such as surgical robots, will enable surgeons to more easily perform minimally-invasive procedures.

Technology that integrates patient information with images generated during surgical procedures or treatments will also improve image-guided approaches. Images, combined with critical information on the patient's current status and history, could be provided to support patient care. Thus, all critical information could be captured immediately at the patient's bedside, at the point of patient care. This can be realized by developing methodologies to integrate data from disparate databases.

Research Advances

MRI-Guided Cardiovascular Interventions. More than one million angioplasty/stent procedures are done annually in the U.S. (American Heart Association 2001 report). This large number of patients with heart and coronary artery disease could benefit from the innovation of minimally-invasive treatments. Minimally-invasive, catheter-based treatments for coronary occlusions have already revolutionized the therapeutic options for treating cardiovascular disease. X-ray techniques are an established method for imaging heart and coronary artery disease and for guiding catheters. However, X-ray imaging may one day be replaced by less hazardous or more informative images from MRI or other imaging technologies. X-ray images, for example, do not allow for the direct visualization of the diseased atherosclerotic tissue. MRI, by comparison, not only images the blood flow in arteries, but can also image the wall of the artery. NIBIB-funded researchers are developing real-time interactive MR imaging systems to diagnose coronary artery disease, and to be used for image-guided interventions and therapies. These systems may be particularly helpful in the treatment of chronic occlusions or identification of non-symptomatic early disease. Other technological advances in imaging and drug-eluting stents may help solve the problem of re-blocking of the coronary arteries.

Integrated Imaging May Improve Epilepsy Surgery. Epilepsy is a brain disorder that produces sometimes frequent and unpredictable seizures. Medication offers relief for most patients, but for the small percentage for whom medication is ineffective, surgical removal of damaged brain tissue may be the best option. A new imaging system now being developed by an interdisciplinary team of NIBIB-funded researchers may shorten surgery times and greatly improve the success rate of this sometimes-risky procedure by allowing surgeons to more precisely pinpoint, and then remove, seizure-causing brain regions. With the new procedure, surgeons can correlate a wide variety of pre-operative brain images, including biochemical information obtained with magnetic resonance spectroscopy and computerized assessments of electrical activity obtained with electrode monitoring. Magnetic resonance images taken prior to surgery are also available by way of pull-down screens in the operating room, along with projected displays of microscope-based images during surgery. Researchers are also beginning to acquire and integrate images representing blood flow in the brain. By co-registering blood flow, electrical activity, and biochemical activity, the surgeon can see more precisely where brain activity is abnormal and avoid damaging brain regions that are critical for functions such as speech. Over the next several years, the research team hopes to develop a neurostimulator that could be implanted in the brain to short-circuit seizures and thus reduce epileptic symptoms. The team’s 10- to 15-year goal is to develop a procedure in which surgeons insert a biosensor along with a drug-delivery system into the brains of epilepsy patients. The system would trigger release of a drug to block seizures before they begin.

Optical Probes May Improve Breast Biopsies. To determine if a breast lump is cancerous, patients often undergo a needle biopsy. One million such diagnostic procedures are performed annually in the U.S. A doctor uses X-ray or ultrasound images to locate suspicious tissue and then retrieves tissue samples with a hollow biopsy needle. The procedure is less invasive, less expensive, and faster than surgical biopsies. Its downside, however, is that it misses as many as 7 percent of cancers. To improve the accuracy of the test, an NIBIB-supported researcher has fitted the biopsy needles with a tiny fiber-optic probe to detect malignant tissues. The probe emits near-infrared light into the breast tissue, and then collects and analyzes light that is not absorbed by the tissue. By monitoring how the light interacts with tissue, the researchers capture structural and physiological information that indicates whether the tissues probed by the needle are malignant. In addition, by simply rotating the needle, the researchers can survey multiple areas in the breast, providing an immediate picture of other suspicious tissue that should be biopsied. The result may mean that women confronting breast cancer will have a more accurate test without the need for additional surgical biopsies. Moreover, the number of cancers that go undetected could be reduced.

Remote Sensing. The quest for more accurate and effective minimally-invasive surgical interventions has resulted in the introduction of computer-assisted robotic technology, whereby the surgeon works under image guidance with small tools through small incisions. This technique is crucial for neonates where organs are delicate and difficult to reach. However, current instrumentation prohibits the surgeon from actually feeling the forces exerted when manipulating tissue. This lack of sensory control can be particularly detrimental in suturing, where the force applied is critical in creating knots that are strong enough to hold, but do not damage tissue. To overcome this problem, NIBIB investigators are developing instruments with 3D sensors designed to give the surgeon a feeling comparable to that of performing the task manually. This research has additional applications as well, including expert-assisted surgery in remote locations.

5-Year Research Agenda

The need to further support research and development in the area of image-guided procedures has been documented at multiple workshops co-sponsored by the NIBIB, including an Image-Guided Interventions Workshop held in May 2004. The goal of this research is the development of tools and technologies that will allow minimally-invasive, image-guided procedures to become the new standards of care. Further development of successful image-guided interventions requires research progress in the following areas:

- Development, optimization, and adoption of new surgical robots, biopsy techniques, and other autonomous devices;
- Improvements in image acquisition for image-guidance monitoring during a procedure;
- Improvements in real-time, 3D imaging, including smart technologies and new tools for 3D visualization;
- Technologies for integrating and fusing images with patient information. For example the integration of images and physiological data in real-time;
- Development of integrated image-guided intervention systems for a wide range of treatments; and
- Technology for image-guided delivery of drugs, genes, and therapeutic devices.

The practice of medicine is shifting from one of disease detection and treatment to one of disease prevention in asymptomatic, at-risk populations. Image-guided interventions allow medical practitioners to look beneath the surface anatomy to visualize the underlying pathology. Image-guided surgical systems will enable surgeons to operate using 3D vision, with minimally-invasive technology, oftentimes at a distance. Surgical tools will be smaller, less expensive, easier to manipulate, and will be seamlessly integrated into the operating room or treatment facility. The field of image-guided interventions is at a critical juncture. The NIBIB will lead the technological advances that will revolutionize patient care.

<u>Technology Development for Molecular Imaging</u>

Radiologists currently detect and diagnose disease by observing disease related size or shape changes in anatomy from images generated by X-ray, nuclear, CT, ultrasound, or MRI. While providing useful clinical information, these anatomical changes often occur late in the disease process. Treatment at the late disease stage often is less effective and more costly. An array of discoveries in the area of cellular and molecular biology cannot be transferred to the clinic because there is no effective way of identifying these molecular or cellular changes in patients. For this reason, the recent development of molecular imaging, with the potential promise of early and more accurate disease diagnosis at the cellular level, has generated great excitement among biomedical imaging scientists and clinicians.

Molecular imaging is the mapping of cellular and molecular activity in normal and disease biomedical processes. Important activities in the body that can be examined using molecular imaging include: tumor growth; stem cell activities; the body’s response to disease and treatment; and cellular production of proteins that are important for health. Molecular imaging may replace tissue biopsies which are invasive and have a high level of inaccuracy. Molecular imaging offers the potential of early and accurate disease diagnosis and more effective disease treatment. Molecular imaging is an extension of the genomic revolution. Imaging of disease markers identified by genomic analysis could lead to tailored therapies to individuals or sub-patient groups - a concept referred to as personalized medicine.

Research Advances
The NIBIB already has a significant research portfolio in optical imaging, MRI, and PET techniques that can be used for molecular imaging studies. The NIBIB also supports a number of projects to develop novel optical and MRI techniques that can be used for new types of molecular imaging studies.

Optical Imaging. NIBIB-supported investigators have developed a number of molecular optical imaging approaches and novel imaging agents that are suitable for molecular imaging. Feasibility studies in animals are promising, but substantial improvements are needed before these technologies can be used for clinical applications in humans. One such approach is optical coherence tomography (OCT). OCT is similar to ultrasound, but relies on using light in near-infrared wavelengths to produce an image rather than using sound waves. Current OCT research supported by NIBIB seeks to develop capacities to identify vulnerable coronary plaques, to improve biopsies of breast cancer, and to accurately guide placement of treatment probes in deep-brain structures for treatment of Parkinson’s disease.

Diffuse Optical Tomography and Fluorescence Tomographic Imaging. While useful, OCT cannot penetrate deep into the human body. NIBIB supports research to image deeper tissue layers using diffuse optical tomography (DOT). Like other optical imaging techniques, DOT does not involve harmful radiation. Researchers supported by the NIBIB seek to image breast tumors non-invasively and to monitor blood oxygen level for stroke management. NIBIB also supports research in fluorescence imaging and fluorescence tomographic imaging for deep tissue imaging. In general, fluorescence imaging allows for *in vivo* tracking of important molecules specifically labeled with a fluorescent dye. Fluorescence tomographic imaging significantly improves the spatial resolution and depth penetration of regular fluorescence imaging. These studies are important because many molecular imaging probes are detected using optical fluorescence. Most developments in fluorescence imaging are currently applied to the study of cancer in animal models.

Imaging Macromolecular Structures. Many diseases can be correlated with abnormalities in the structure of cells. For example, amyloid plaques indicate Alzheimer's disease and many liver diseases are associated with fibrous collagen deposits. Current imaging techniques cannot be used to detect and characterize these abnormal structures. This is done only after they have been biopsied and analyzed. New imaging modalities are being developed, such as multiphoton microscopy, that enables researchers to study living cells and tissues without inflicting significant damage.

Increased Sensitivity and Resolution. MRI is a powerful imaging technique but could benefit from additional improvements and technological advances. For example, MRI is not adequate for seeing cell sized structures. The NIBIB is currently funding a number of studies to provide technological solutions to overcome these limitations. An example is the development of new magnetic resonance spectroscopic imaging approaches to allow improved quantitation of the amounts or proportions of intracellular biochemical metabolites. Development in electron paramagnetic resonance (EPR) imaging supported by the NIBIB seeks to non-invasively obtain images of important physiological parameters such as oxygen tension and nitric oxide concentrations. This research could lead to new insights into stroke and tumor growth.

Multi-Modality Approaches to Imaging. Many molecular imaging approaches that provide information about normal or disease processes do not provide adequate information about anatomical structures within the body at the same time. The NIBIB currently supports a number of studies that combine molecular imaging approaches, such as optical imaging and EPR imaging with MRI. These integrated systems allow simultaneous anatomic and molecular imaging with the potential for precisely relating molecular activities and anatomy. The ability to precisely relate molecular activity with anatomy is crucial for clinical applications of molecular imaging approaches.

5-Year Research Agenda

In the last 5 years, a number of molecular imaging techniques have been developed and tested in small laboratory animals. Over the next 5 years, the challenge is to extend these techniques to humans and to demonstrate that they can be successfully used in clinical situations. Extension of molecular imaging techniques to humans will require progress in two areas:

- Improvements in scanners for optical, MRI, ultrasound, X-ray, CT, and PET. In all cases, the human scanners will have to be dramatically improved, with the overall sensitivity improved by at least two or three orders of magnitude; and

- Identification of specific disease markers – molecules that are related to the disease processes. Molecular imaging combines new molecular agents with traditional imaging tools to capture pictures of specific biological pathways and processes in the body.

Improved scanners will undoubtedly impact many areas of medicine. Most likely, the development of new imaging agents will be tied to specific diseases and organ systems. Therefore, this research will be coordinated through close collaborations with the disease-specific Institutes at the NIH. For example, the NIBIB and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) co-sponsored a joint workshop entitled “Imaging the Pancreatic Beta Cell.” The workshop explored the potential of molecular imaging approaches in clinical studies of diabetes. The NIBIB, the NIDDK and the National Cancer Institute (NCI) co-sponsored another workshop entitled, “Hepatocellular Carcinoma: Screening, Diagnosis and Management.” This workshop explored the potential of molecular imaging approaches in clinical studies of liver cancer. The information obtained from these two workshops provided invaluable guidance in planning future NIBIB research initiatives in technology development for molecular imaging.

Molecular imaging can be applied to speed up the drug development process and thereby significantly reduce the cost of new drugs. Instead of relying on patient survival rate as the ultimate guide for clinical efficacy, molecular imaging may provide specific information on how the patients respond to experimental drug. Molecular imaging can therefore be applied in drug development clinical trials to expediently rule out drug candidates that do not work at the cellular and molecular level. As the average cost for developing a successful new drug is substantial, this could translate into significant savings in the annual health care budget.

Over the next 5 years, molecular imaging has the potential to move into the clinical environment, leading to earlier and more accurate diagnosis of disease and to personalized medicine.

Sensors and Microsystems

Empowering clinicians to make decisions at the “point-of-care” has the potential to significantly impact the quality of healthcare delivery. The ability to provide rapid assessment of a patient’s health in a non-laboratory setting relies on the use of small, portable devices that can be used by clinicians to analyze blood, saliva, and other biological samples. The NIBIB has contributed to advances in this area by funding the development of sensor and microsystem technologies for point-of-care testing. These instruments combine multiple analytical functions into self-contained devices that can be used by non-specialists to detect and diagnose disease, and can enable the selection of optimal therapies through patient screening and monitoring of a patient’s response to a chosen treatment. In specific cases, sensors and microsystems can enable patient self-testing, and can contribute to the realization of personalized medicine by creating a link between the diagnosis of disease and the ability to tailor therapeutics to the individual. These technological advances limit the reliance on submission of samples to centralized laboratories, with results available within minutes as opposed to several hours or days, enabling clinicians to make decisions regarding treatment at a time when these decisions can have the greatest impact.

Research on sensors and microsystems is currently focused on the design of more sensitive devices that enable the detection of an increasingly smaller number of disease-related substances in a given sample, which could provide earlier stage information regarding the presence of disease. A second area of emphasis is on miniaturizing existing technologies and integrating multiple components into single devices for the creation of micro-total analysis systems (microTAS), or “lab-on-a-chip” devices, with the goal of incorporating functions of a full-sized laboratory into a handheld instrument. A potential benefit of microTAS devices is the ability to analyze small samples, which could have a significant impact in critical care, where repeated collection of large samples from the patient (e.g., a neonate) can have adverse effects. Additional benefits include limited reagent use, faster sample analysis, increased sensitivity, automation of complex analytical processes, ease of use and portability.

Research Advances

Significant progress has been made over the past several years in the development of sensors and microsystems for clinical laboratory diagnostics. Sensor technologies have been developed for the rapid analysis of blood samples for several critical care assays, including blood chemistry, electrolytes, blood gases and hematology. Biosensors are currently being used clinically for toxicology and drug screens, measurement of hematocrit and blood coagulation, bedside diagnosis of heart disease through detection of cardiac markers in the blood, and glucose self-testing. A variety of systems have been developed for DNA analysis, with increased interest in applying technological advances to the detection of other clinically relevant substances, such as proteins and carbohydrates.

Improved Sensitivity. NIBIB-supported investigators are improving the sensitivity of sensor devices, pushing the limits of single cell or even single molecule detection. Increased sensitivity of clinical diagnostic sensors can improve detection of a disease, allowing earlier intervention. Advances in this area have been possible through the application of nanotechnology, with researchers achieving unprecedented levels of sensitivity through the use of nanoparticles and nanotubes. Other researchers are pursuing label-free biosensors, which provide sensitive approaches to disease detection without the need to attach tags, or labels, to the biomolecules of interest.

High Throughput Analysis. Large-scale screening and analysis of biological samples is becoming possible through the development of sensor arrays, including microarrays and nanoarrays, that can be used to analyze a wide range of biological substances simultaneously. Technological developments in this area will enable clinicians to assess a patient’s predisposition to disease, and will provide the clinician with tools to improve the diagnosis of disease and tailor the choice of therapy for an individual. This technology relies on placing or printing biomolecules onto specific locations on the surface of a glass slide or other material. Advances in higher resolution printing technologies, with parallel improvements in the ability to read information from the arrays, are pushing the technologies toward higher throughput capabilities.

Miniaturization and Integration. Research in the area of microsystems has significantly increased over the past several years, with new applications emerging in basic research, diagnostics, and therapeutics. Recent studies have focused on the microfabrication of devices using polymer-based approaches that are more suitable for the handling of biological substances. Advances have been made in overcoming the challenges unique to microsystems, such as: fluid control and mixing; detection specificity and sensitivity; and processing speed. New systems are emerging, especially in the area of DNA analysis, that are capable of handling sample preparation, mixing, chemical reactions and detection all on a single chip, with the promise of self-contained portable devices that can be used for rapid assessment of a patient's health.

5-Year Research Agenda
The NIBIB complements the efforts of the disease- and organ-specific Institutes at the NIH through funding the development of novel technologies that can be applied to the diagnosis and treatment of disease. For sensor and microsystems, this effort is directed toward providing technology platforms for clinical application of research focused on the identification and validation of biomarkers of disease. As new biological links to disease are discovered, tools must be developed to enable the application of this knowledge to the detection and diagnosis of disease in a clinical setting. Several specific themes are emerging:

- *Integrated Microsystems for Point-of-Care Applications*. Recent advances in the design and microfabrication of electronic, optical, mechanical, and fluidic components for sensors have enabled fundamental studies of biosensing platforms. Yet the incorporation of the respective components into fully integrated systems that can handle all aspects of analysis still remains challenging. A recent World Technology Evaluation Center study on International Research and Development in Biosensing, funded in part by the NIH, found that few laboratories are attempting to address these challenges, with such work requiring significant financial resources, a high level of technical sophistication, and a coupling of diverse technical disciplines. With links to both the engineering and biomedical communities, the NIBIB is uniquely suited to encourage development in this area. The goal of funding in this area is to stimulate development of integrated microsystems capable of providing sample-to-answer capability for the creation of truly portable, self-contained devices that will have a significant impact in the clinical setting.

- *Microsystems for Single-Cell Analysis*. Current research is shifting to the analysis of increasingly complex samples. Applications in the area of single cell analysis are emerging that have the potential to shed light on the variability of biological and disease processes in cells. With single cell analysis, there is the added challenge of working with very small volumes and limited numbers of biomolecules within a given cell. The scale of microsystems is well-suited for cellular systems, although detection limits, sample handling, and sample preparation become critical issues that must be addressed. Additional concerns include designing the interface between cell and sensor surfaces that preserve the biological response, developing novel detection schemes that report on cellular responses, and integrating the biological and microsystem components. With advances in this area, single cell analysis can become a useful tool for diagnosing disease at a stage when changes on a tissue level are not yet evident but chemical changes within cells are observable.

Nanotechnology and Drug Delivery

Drug therapy is a key facet of medical treatment for both acute and chronic diseases. With the explosion of new therapeutic agents, it is easy to lose sight of the fact that drug delivery to the correct anatomical site, in the appropriate dose and at the right time, is as critical to successful treatment as is drug choice. The two most common methods of drug delivery used today are oral and parenteral (injection). Drugs taken orally are currently limited to small molecules because therapeutic agents based on large biological molecules, such as proteins, (e.g. insulin for the control of blood sugar), are degraded by the digestive system. However, drugs based on small molecules can be non-specific, high in toxicity, and low in bioavailability (rapidly cleared from the body). These factors can lead to significant side effects. One example is the anti-cancer drug paclitaxel. Paclitaxel is a potent drug used in chemotherapy for breast cancer that interferes with the growth of cancer cells but is very toxic. Because the growth of normal cells may also be affected by paclitaxel, the ability to target the drug only to tumor cells is critical to the safe and efficacious use of the drug. Supporting the research and development of new drug carrier systems that can localize the delivery of drugs like paclitaxel to only tumor cells while minimizing toxicity and side effects is an ongoing priority for the NIBIB. Another major focus is the development of new delivery technologies that will allow protein drugs such as insulin to be taken in pill form instead of painful injections.

Research Advances
The emergence of nanotechnology - the branch of engineering that deals with things smaller than 100 nanometers - has opened a new era of design-driven research into the development of “smart” drug delivery systems. These delivery systems can potentially package highly potent drugs and target specific diseased tissues or cells while minimizing side effects.

Increasing Bioavailability. Drugs that are administered by injection are often cleared from the body before they reach or accumulate in the targeted tissues. Among the promising approaches to address this problem are the design and synthesis of new nanometer size drug carrier vehicles with surface structures that mimic those of native cells. These carriers allow the drug to remain in circulation by delaying or avoiding elimination or destruction by the body until the drug can accumulate in the targeted tissues.

Increasing Solubility. The solubility of hydrophobic, or poorly water soluble, drugs can be improved by impregnating these drugs in multi-layer nanoparticles with hydrophobic cores. The nanometer size of these particles also facilitates their uptake by cells because of the relative size differences (drug carrying nanoparticles can be 1000 times smaller than the target cell in diseased tissues). Using this approach, NIBIB-supported researchers continue to improve the clinical effectiveness of existing drugs by enabling larger and more effective dosing of poorly soluble drugs while minimizing adverse side effects.

Targeted Delivery. The ability to target the delivery of a therapeutic agent to a specific organ or tissue can greatly reduce side effects associated with systemic dosing. The new generation of designed nanoparticles can be labeled with targeting elements that attach to specific sites on the surface of cells and facilitate entry into the cell. One example is the attachment of ligands (bound molecules) to the surface of nanoparticles which confer the ability to bind specifically to receptors that are abundant only in targeted cells such as tumor cells for the delivery of anticancer agents or targeted tissues for gene therapy.

Protein Delivery. Proteins and other high molecular weight (macromolecular) biopolymers are an important class of therapeutic agents that are limited to intravenous or intramuscular injection due to degradation by stomach acid and enzymes in the digestive tract. The ability to deliver these molecules intact orally would have a high impact on the treatment of diseases such as type 1 diabetes which currently requires intramuscular injection of insulin. The NIBIB presently supports research on new technological approaches for the delivery of large molecule therapeutic agents. One approach utilizes bioresponsive polymers as drug carriers that can change shape in response to the acidity of the surrounding environment. These new materials shield acid sensitive drugs during passage through the stomach and can selectively attach and deliver their payloads to the mucosal lining of the small intestine for release into the blood stream. These types of approaches may enable the full potential of protein based drugs for the treatment of diseases in the near future.

5-Year Research Agenda

The examples of advances in delivery technologies described above are the result of design-driven synthesis of new molecules and devices at the nanoscale. The way in which these new nanostructures are synthesized is still based on traditional chemical methods. The pace at which smart drug delivery systems are developed and commercialized could be greatly accelerated by improved fabrication methods at the nanoscale that allow the rapid and efficient synthesis of complex molecular structures. Examples of research areas that would contribute to the achievement of this critical enabling technology are:

- New methods for the manufacture of nanoscale components and systems using top-down, self-assembly, biomimetic, or other approaches;

- Tools for manipulation and assembly of nanoscale components;

- Measurement tools for the 3D measurement and characterization of nanoscale materials, components, and systems;

- Systems integration for signal and data management that bridges output from nanoscale components to macroscale interfaces; and

- Simulation and modeling tools to enable the development of computer-aided design and computer-aided manufacture processes that can operate continuously from the macro control level to the nano actuation level.

Tissue Engineering

Tissue engineering is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. It also offers the potential for the development of human tissues to study developmental biology, physiology and disease pathogenesis. In addition, engineered 3D human tissues could be used as a better model system than current animal models for the development and screening of new drug candidates, identification of novel genes as drug targets or therapeutic agents, and testing for drug toxicity. As an emerging multidisciplinary field at the interface between the life and physical sciences, there is significant need for the NIBIB to provide additional resources to foster the science needed for this field to mature and for translation of important breakthroughs from basic research to clinical studies and ultimately to patients.

Research Advances

Significant clinical advances have been made in the engineering of structural tissues including skin, bone, and cartilage. With several products on the market, skin is the most successfully engineered tissue, which has been used for skin replacement, temporary wound cover for burns, and treatment for diabetic leg and foot ulcers. Advances in bone and cartilage tissue engineering include the use of tissue engineered products to induce bone and connective tissue growth, guide long bone regeneration, and replace damaged knee cartilage. Vascular grafts for heart bypass surgery and cardiovascular disease treatment currently remain at the pre-clinical trial stage. Metabolic tissues such as kidney, pancreas, and liver have more complicated functional roles in the human body and hence pose bigger challenges for tissue engineering. Cell-containing bioreactors such as a bioartificial liver and kidney have been developed in laboratories to substitute for failed organs. Other clinical research efforts focus on the development of bladder, cornea, nerve, blood, and blood components. One of the major long term goals is for tissue engineered organs to significantly alleviate the current organ transplantation crisis.

Research and technology development in tissue engineering promises to revolutionize current methods of health care treatment and significantly improve the quality of life for millions of patients. The NIBIB contributes to advances in this area by supporting research on biomaterials, cell growth and differentiation, cell-biomaterial interfaces, and tool development.

Cells. Cells are the basic functional units of tissues. Understanding of their self-assembly into tissues and then into organs is one of the fundamental challenges in tissue engineering. NIBIB-supported investigators and others have been focused on understanding cell function and cell signaling pathways; optimizing cell sources for tissue engineering; defining better culture conditions to grow and expand cells; controlling cell differentiation by molecules such as growth factors as well as electrical and mechanical stimuli; and understanding the interactions of cells with their environment. Advances in stem cell research and the success of the human genome project have also led to further understanding of cells.

Biomaterials. A simple view of tissues is that they are composed of cells and structural supports for the cells, i.e. extracellular matrix (ECM). Interactions between cells and the ECM are critical in defining tissue structure and function. Biomaterials are often used as an alternative ECM in tissue engineering to provide structural support. Advances in this area include the modification of existing materials to mimic the ECM and the use of nanotechnology such as nano-patterning to guide cell patterning.

Tools. Recent advances in imaging technologies, high-throughput assays and instrumentation, computer modeling, and bioinformatics have provided revolutionary tools for many areas of science. Their applications to tissue engineering, however, have been very limited. NIBIB-supported investigators are beginning to develop and/or adapt different imaging techniques to non-invasively and non-destructively track the function of engineered tissue in real-time. Other investigators are trying to improve cell preservation technologies to make possible engineered tissues that are readily available to patients. Additional work is being supported in the design of bioreactors for growing the tissue so that the environment is a better approximation of the physiological environment in which tissues normally grow.

5-Year Research Agenda

There are many challenges to overcome before “off-the-shelf” tissues can be created for use as therapies for patients. The NIBIB will support the following major areas relevant to its mission:

- *Novel Scaffolds for Tissue Development*. To effectively guide the organization, growth, and differentiation of cells in tissue engineered constructs, new biomaterial scaffolds will be necessary. These materials must be able to provide structural support as well as the physical, chemical, and mechanical cues necessary for forming functional tissues. This structural and functional framework in the human body is known generally as the extracellular matrix (ECM). Artificial substitutes for ECM are referred to as scaffolds. Research is needed to support the development of novel biomaterials capable of generating scaffolds that more closely mimic the ECM. These materials, and their degradation products, must be non-toxic and non-immunogenic, as well as possess other properties specific for a given tissue construct at the site of implantation. Advances in this field will depend not only on the development of novel biomaterials but also on an increased understanding of how these materials interact with cells.

- *Design of Functional Engineered Tissues*. Advances are needed in the application of rational engineering design principles to functional engineered tissues. The design must span multiple hierarchical scales, from the macroscopic level, directed at satisfying the clinical requirements of the product, to the microscopic level, directed at satisfying the cell and molecular requirements. Rational design offers a cost-effective approach for tissue engineering. It will likely require advances in the integration of experimental results with computer-aided technologies including design, image visualization and reconstruction, modeling, simulation, optimization, and tissue informatics.

- *Enabling Technologies for Tissue Engineering*. In order to realize the full potential of tissue engineering, researchers must be able to develop safe and efficacious products for patients. A wide range of enabling technologies are required to accomplish this goal. Examples include real-time, non-invasive tools for assessing the function of engineered tissues; high-throughput assays and instruments to reduce the cost, time, and complexity of tissue engineering; bioreactor techniques for growing tissues and organs on a commercial scale; the development of pre-clinical models and methods for testing biosafety, quality assurance and performance; and strategies for preserving living tissue products.

Building and Maintaining Interdisciplinary Training Programs

The NIBIB conducts and supports a number of training and career development programs that address workforce needs in biomedical imaging and bioengineering. A major focus of the Institute's training and career development programs is the support of interdisciplinary approaches that integrate the quantitative and engineering sciences with the life sciences and clinical medicine. The NIBIB serves as a training and career development resource for a burgeoning community of researchers who will lead the technological advances that will be critical to address important public health problems. It takes a new "breed" of scientist to integrate the engineering and physical science aspects of these problems with the biology and medicine. The NIBIB is poised to serve as a focal point for training of this new and critical generation of scientists.

The NIBIB has joined a number of existing trans-NIH funding mechanisms and approaches. However, a number of innovative programs have been initiated or are envisioned to further meet the needs specific to the Institute's extramural community. These training and career development approaches are necessary to achieve the mission of the NIBIB and to foster a new cadre of scientists who can approach research questions of biomedical health from an interdisciplinary perspective. Innovative programs include:

- *HHMI-NIBIB Interfaces Initiative for Interdisciplinary Graduate Research Training*. The Howard Hughes Medical Institute (HHMI) and the NIBIB recently teamed up in a novel public-private partnership to stimulate the development of new interdisciplinary graduate training programs that integrate the physical, quantitative, and engineering sciences with the life sciences. This program will be conducted in two phases and is designed to build on the strengths of each organization.

- *Supplements for Clinical Residents to Conduct Technology-Based Research.* In order to address research questions at the interface of technology and medicine, it is important to attract physicians to research careers. The NIBIB released an initiative to recruit clinical residents to research careers by providing an opportunity for NIBIB-funded investigators to develop a specific project for these individuals. Because of the interdisciplinary nature of biomedical imaging and bioengineering research, the National Advisory Council for Biomedical Imaging and Bioengineering has recommended that NIBIB not limit applications to only NIBIB investigators, but rather solicit applications from all NIH-funded investigators.

- *Faculty Transition Awards*. A critical period in the development of a scientist is the transition from a postdoctoral fellowship to a faculty position. This program would provide a "bridge" for newly independent scientists to establish their careers and to move forward in conducting interdisciplinary technology-based research.

Five-Year Professional Judgment Budget

The NIBIB mission supports research on a broad range of technologies from molecular imaging to systems for integrating imaging data from multiple sources; from development of new drug delivery systems to research on the development of tissue engineered systems; and from development of "one-of-a-kind" imaging research tools to development of low-cost imaging and diagnostic technologies that could be widely deployed in rural and inner city environments. The unifying ideas that bind these areas of research is that they are all at the interface of the physical and life sciences, have strong potential to improve human health, and present significant opportunities at the present time. This five-year professional judgment budget would allow execution of the research agendas as outlined and accelerate the translation of these developments into practical benefits for mankind.

The research community, and particularly the engineering and physical science research community, has reacted with enthusiasm to NIBIB's strategic plan. In 2003, NIBIB released ten new initiatives and received 1,074 applications in response to these requests for applications (RFA).

Over the past 3 years the number of applications received has been 1,500, 863, and 980 for 2003, 2004, and 2005, respectively. To estimate the growth in applications that are not in response to specific funded initiatives, we counted the number of grants not associated with an RFA or a program announcement with funds set aside (PAS). Of the 1,500 total applications the NIBIB received in 2003, 400 of those were not in response to an RFA or PAS. Over the past 2 years, growth in these applications not associated with a funded initiative has been vigorous. For 2004, the growth was over 100 percent and the projected growth rate for these applications received in 2005 based on recent data is approximately 20 percent. A significant portion of this growth is coming from investigators new to the NIH.

Based on the success in drawing new investigators to the NIH research enterprise and the number of research areas that are ripe for development, the following professional judgment budget provides reasonable growth for this developing Institute. The budget increase presented below has two key components. First, it provides funds to support two new initiatives per year over the next five years. This will permit expanded development of the most promising areas of research. Second, it provides growth in funding commensurate with the increasing number of applications from researchers in the imaging, engineering, and physical sciences who are addressing health care problems. This second component of the funding increase will help NIBIB maintain a success rate for research project grants (RPG) comparable to the rates for other NIH Institutes that will encourage new investigators to participate and capitalize on their ideas and expertise. (In FY 2004, NIBIB has an RPG success rate of 16.7 percent compared with 24.6 percent overall at NIH). Consistent with the legislative language that created NIBIB that states "basic research in imaging, bioengineering, computer science, informatics, and related fields is critical to improving health care but is fundamentally different from the research in molecular biology on which the current national research institutes at the National Institutes of Health are based," the NIBIB is drawing significant numbers of new investigators into the NIH research enterprise and plans to continue this trend.

NIBIB’s five-year professional judgment budget is as follows:

FY 2002 Appropriation	$112 million
FY 2003 Appropriation	$278 million
FY 2004 Appropriation	$287 million
FY 2005 Appropriation	$298 million
FY 2006 Estimate	$340 million
FY 2007 Estimate	$388 million
FY 2008 Estimate	$442 million
FY 2009 Estimate	$504 million
FY 2010 Estimate	$575 million

It must be noted that this estimate is based on an assessment of scientific opportunities over the next five years, without consideration of economic constraints, unforeseeable scientific advances, or other competing priorities of the Federal government.

Conclusion

The fields of biomedical imaging and bioengineering are expanding rapidly – from the detection, diagnosis, and treatment of diseases and disabilities at the level of tissues and organs to the analysis of structure and function at the molecular and genetic levels. The establishment of NIBIB was predicated on present and potential advances in these exciting fields. As the Institute evolves in the coming years, the research mission and vision will guide the NIBIB to capitalize on emerging scientific areas where biomedical imaging and bioengineering approaches can be used to advance the practice of medicine. This professional judgment budget would enable the NIBIB to accelerate discoveries and create and capitalize on opportunities to profoundly improve health care. Focus is on discovery, development and the translation of research findings from the laboratory into practical solutions of clinical problems. This will advance human health, reduce the burden of disease, and improve the quality of life.